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(54) Title: 7–DEOXY–6–NITROGEN SUBSTITUTED PACLITAXELS

(57) Abstract

The present invention concerns novel paclitaxel derivatives, their use as antitumor agents, and pharmaceutical formulations.

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7-DEOXY-6-NITROGEN SUBSTITUTED PACLITAXELS

BACKGROUND OF THE INVENTION

Field of the Invention

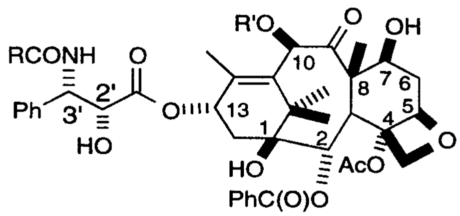
The present invention concerns antitumor compounds. More particularly, the invention provides novel paclitaxel derivatives, pharmaceutical formulations thereof, and their use as antitumor agents.

Background Art

Taxol® (paclitaxel) is a natural product extracted from the bark of Pacific yew trees, Taxus brevifolia. It has been shown to have excellent antitumor activity in in vivo animal models, and recent studies have elucidated its unique mode of action, which involves abnormal polymerization of tubulin and disruption of mitosis. It has recently been approved for the treatment of refractory advanced ovarian cancer and breast cancer; and studies involving other cancers have shown promising results. The results of paclitaxel clinical studies are reviewed by numerous authors, such as by Rowinsky and Donehower in "The Clinical Pharmacology and Use of Antimicrotubule Agents in Cancer Chemotherapeutics," Pharmac. Ther., **52**:35-84, 1991; by Spencer and Faulds in "**Paclitaxel**, A Review of its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Potential in the Treatment of Cancer," Drugs, 48 (5) 794-847, 1994; by K.C. Nicolaou et al. in "Chemistry and Biology of Taxol," Angew. Chem., Int. Ed. Engl., **33**: 15-44, 1994; by F.A. Holmes, A.P. Kudelka, J.J. Kavanaugh, M. H. Huber, J. A. Ajani, V. Valero in the book "Taxane Anticancer Agents Basic Science and Current Status" edited by Gunda I. Georg, Thomas T. Chen, Iwao Ojima, and Dolotrai M. Vyas, 1995, American Chemical Society, Washington, DC, 31-57; by Susan G. Arbuck and Barbara Blaylock in the book "TAXOL® Science and Applications" edited by Mathew Suffness, 1995, CRC Press Inc., Boca Raton, Florida, 379-416; and also in the references cited therein.

A semi-synthetic analog of paclitaxel named Taxotere® (docetaxel) has also been found to have good antitumor activity. The structures of

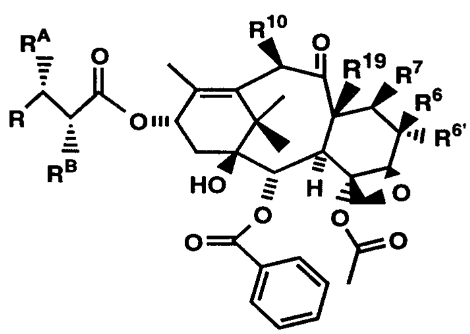
paclitaxel and Taxotere® are shown below along with the conventional numbering system for molecules belonging to the class; such numbering system is also employed in this application.



Taxol®: R = Ph; R' = acetyl
Taxotere®: R = t-butoxy; R' = hydrogen

SUMMARY OF THE INVENTION

This invention describes novel antitumor compounds in which the C-6 position of the taxane core is linked by a direct bond to a nitrogen atom. This invention relates to novel antitumor compounds represented by formula I, or pharmaceutically acceptable salt thereof



I

wherein R is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, cyclic 3-7 membered ring containing either one or two heteroatoms, heteroaryl or $-Z^1-R^3$;

Z^1 is a direct bond, C_{1-6} alkyl, or $-O-C_{1-6}$ alkyl;

R^3 is aryl, substituted aryl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, cyclic 3-7 membered ring containing either one or two heteroatoms, or heteroaryl;

R^A is -NHC(O)R, -NHC(O)OR, -NHC(O)NHR, $-NHC(O)N(R)_2$, $-NHS(O)_mR$, $-NHP(=O)(OR)_2$, $-NHP=S(OR)_2$, where m is 1 or 2;

R^B is hydroxy, fluoro, $-OC(O)R^x$, $-OC(O)OR^x$, $OP(O)(OH)_2$, $OCH_2OP(O)(OH)_2$, $-OCH_2OCH_2OP(=O)(OH)_2$, $OP(O)(OH)_2$ base, $OCH_2OP(O)(OH)_2$ base, $-OCH_2OCH_2OP(=O)(OH)_2$ base, $-(OCH_2)_mOC=OCH_2NHR^x$, $-(OCH_2)_mOC(=O)CH(R'')NR'_6R'_7$ where m is 0-3, $-OCOCH_2CH_2NH_3^+\ HCOO^-$, $-OCOCH_2CH_2COOH$, $-OCO(CH_2)_3COOH$, $-OC(O)(CH_2)_nNR^FR^G$, where n is 0-3, $-OC(O)CH_2CH_2C(O)OCH_2CH_2OH$ or -OC(O)-Z-C(O)-R';

Z is ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$), -CH=CH-, 1,2-cyclohexane or 1,2-phenylene;

R' is -OH, -OH base, $-NR'_2R'_3$, $-OR'_3$, $-SR'_3$ or $-OCH_2C(O)NR'_4R'_5$;

R'_2 is -H or $-CH_3$;

R'_3 is $-(CH_2)_nNR'_6R'_7$ or $(CH_2)_nN^+R'_6R'_7R'_8X^-$, where n is 1-3;

R'_4 is -H or $-C_1-C_4$ alkyl;

R'_5 is -H, $-C_1-C_4$ alkyl, benzyl, hydroxyethyl, $-CH_2CO_2H$ or dimethylaminoethyl;

R'_6 and R'_7 are independently -H, $-CH_3$, $-CH_2CH_3$, benzyl or R'_6 and R'_7 together with the nitrogen of $NR'_6R'_7$ form a pyrrolidino, piperidino, morpholino, or N-methylpiperizino group;

R'_8 is $-CH_3$, $-CH_2CH_3$ or benzyl;

X^- is halide;

base is NH_3, $(HOC_2H_4)_3N$, $N(CH_3)_3$, $CH_3N(C_2H_4)_2NH$, $NH_2(CH_2)_6NH_2$, N-methylglucamine, NaOH or KOH;

R^F and R^G are independently -H or -C_1-C_3 alkyl, or R^F and R^G taken together with the nitrogen of NR^FR^G form a pyrrolidino, piperidino, morpholino or N-methylpiperizino groups;

R″ is -H, -CH_3, -$CH_2CH(CH_3)_2$, -$CH(CH_3)CH_2CH_3$, -$CH(CH_3)_2$, -CH_2phenyl, -$(CH_2)_3NH_2$, -$(CH_2)_4NH_2$, -CH_2CH_2COOH, -$(CH_2)_3NHC(=NH)NH_2$, the residue of the amino acid proline, -$OC(O)CH=CH_2$, -$C(O)CH_2CH_2C(O)NHCH_2CH_2SO_3$-Y+ or -$OC(O)CH_2CH_2C(O)NHCH_2CH_2CH_2SO_3$-Y+;

Y+ is Na+ or N+$(Bu)_4$;

R^6 and $R^{6'}$ are independently hydrogen, N_3, NH_2, NHR, $N(R)_2$, NHC(O)R, NHC(O)OR, NHC(O)NHR, $NHC(O)N(R)_2$, $NHSO_2R$, NHS(O)R, $NHPO_2OR$, $NHPO_2NHR$ or NR_aR_b where R_a and R_b together with the nitrogen atom form a heteroaryl ring or a heterocyclic ring;

R^7 is hydrogen;

R^{19} is methyl;

R^{10} is hydrogen, hydroxy, -$OC(O)R^x$, -$OC(O)OR^x$, -O-C_{1-6} alkyl, -OCH_2OCH_3, -$OCH_2OCH_2OCH_3$, -$OCH_2OCH_2OCH_2CH_3$, -$OCH_2OCH_2CH_2OCH_3$, -$OCH_2OCH_2CH_2OH$, -OCH_2SR, -$OCH_2OCH_2SCH_3$, -$OC(O)NR'_6R'_7$, C_{1-6} alkyl, -$(CH_2)_3C(O)R^x$, -$(CH_2)_3C(O)OR^x$, -$(CH_2)_3CN$,-$OP(O)(OH)_2$, -$OCH_2OP(O)(OH)_2$, -$OCH_2OCH_2OP(O)(OH)_2$, -$(OCH_2)_nOC=OCH_2NHR^x$, -$(OCH_2)_nOC(=O)CH(R'')NR'_6R'_7$, where n is 0-3, -$OCOCH_2CH_2NH_3^+$ $HCOO^-$, -$OCOCH_2CH_2COOH$, -$OCO(CH_2)_3COOH$, -OC(O)-Z-C(O)-R′, -$OC(O)(CH_2)_nNR^FR^G$ where n is 0-3, or -$OC(O)CH_2CH_2C(O)OCH_2CH_2OH$; and

R^X is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cyclo alkyl, any of which groups can be optionally substituted with one to six of the same or different halogen atoms or with one or more hydroxy groups.

A preferred embodiment are compounds wherein

R is phenyl, p-fluorophenyl, p-chlorophenyl, p-Tolyl, isopropyl, isopropenyl, isobutenyl, isobutyl, cyclopropyl, furyl, or thienyl;

R^A is -NHC(O)Ph, or -NHC(O)O-(C_{1-6} alkyl);

R^B is hydroxy;

R^2 is phenyl;

R^4 is methyl;

R^9 and $R^{9'}$ together form an oxo (keto) group;

R^{10} is hydroxy or -OC(O)CH_3; and

R^{19} is methyl.

An even more preferred embodiment are compounds wherein

R is phenyl or p-fluorophenyl;

R^A is -NHC(O)Ph, NHC(O)O-*t*- butyl or -NHC(O)O-isopropyl;

$R^{6'}$ is hydrogen; and

R^{10} is -OC(O)CH_3.

Another aspect of the present invention provides a method for inhibiting tumor in a mammalian host which comprises administering to said mammalian host an antitumor effective amount of a compound of formula I.

Yet, another aspect of the present invention provides a pharmaceutical formulation which comprises an antitumor effective amount of a compound of formula I in combination with one or more pharmaceutically acceptable carriers, excipients, diluents or adjuvants.

DETAILED DESCRIPTION

In the application, unless otherwise specified explicitly or in context, the following definitions apply. The numbers in the subscript after the symbol "C" define the number of carbon atoms a particular group can contain. For example "C_{1-6} alkyl" means a straight or branched saturated carbon chain having from one to six carbon atoms; examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, t-butyl, n-pentyl, sec-pentyl, isopentyl, and n-hexyl. Depending on the context, "C_{1-6} alkyl" can also refer to C_{1-6} alkylene which bridges two groups; examples include propane-1,3-diyl, butane-1,4-diyl, 2-methyl-butane-1,4-diyl, etc. "C_{2-6} alkenyl" means a straight or branched carbon chain having at least one carbon-carbon double bond, and having from two to six carbon atoms; examples include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl, and hexenyl. Depending on the context, "C_{2-6} alkenyl" can also refer to C_{2-6} alkenediyl which bridges two groups; examples include ethylene-1,2-diyl (vinylene), 2-methyl-2-butene-1,4-diyl, 2-hexene-1,6-diyl, etc. "C_{2-6} alkynyl" means a straight or branched carbon chain having at least one carbon-carbon triple bond, and from two to six carbon atoms; examples include ethynyl, propynyl, butynyl, and hexynyl.

"Aryl" means aromatic hydrocarbon having from six to ten carbon atoms; examples include phenyl and naphthyl. "Substituted aryl" means aryl independently substituted with one to five (but preferably one to three) groups selected from C_{1-6} alkanoyloxy, hydroxy, halogen, C_{1-6} alkyl, trifluoromethyl, C_{1-6} alkoxy, aryl, C_{2-6} alkenyl, C_{1-6} alkanoyl, nitro, amino, cyano, azido, C_{1-6} alkylamino, di-C_{1-6} alkylamino, and amido. "Halogen" means fluorine, chlorine, bromine, and iodine.

"Heterocyclic" means a 3 to 6-membered non-aromatic ring containing at least one and up to three non-carbon atoms selected from oxygen, sulfur and nitrogen. Examples include piperadine, pyrrolidine, morpholine, piperazine and like rings.

"Heteroaryl" means a five- or six-membered aromatic ring containing at least one and up to four non-carbon atoms selected from oxygen, sulfur and nitrogen. Examples of heteroaryl include thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl,

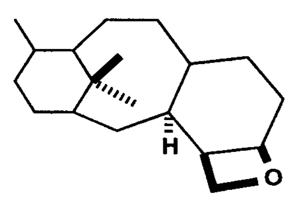
isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, thiatriazolyl, oxatriazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, tetrazinyl, and like rings.

"Hydroxy protecting groups" include, but is not limited to, ethers such as methyl, t-butyl, benzyl, p-methoxybenzyl, p-nitrobenzyl, allyl, trityl, methoxymethyl, methoxyethoxymethyl, ethoxyethyl, tetrahydropyranyl, tetrahydrothiopyranyl, dialkylsilylethers, such as dimethylsilyl ether, and trialkylsilyl ethers such as trimethylsilyl ether, triethylsilyl ether, and t-butyldimethylsilyl ether; esters such as benzoyl, acetyl, phenylacetyl, formyl, mono-, di-, and trihaloacetyl such as chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl; and carbonates such as methyl, ethyl, 2,2,2-trichloroethyl, allyl, benzyl, and p-nitrophenyl. Additional examples of hydroxy protecting groups may be found in standard reference works such as Greene and Wuts, Protective Groups in Organic Synthesis, 2d Ed., 1991, John Wiley & Sons, and McOmie; and Protective Groups in Organic Chemistry, 1975, Plenum Press.

"Ph" means phenyl; "ipr" means isopropyl; "DAST" means diethylamino sulfur trifluoride.

The substituents of the substituted alkyl, alkenyl, alkynyl, aryl, heterocyclic and heteroaryl groups and moieties described herein, may be alkyl, alkenyl, alkynyl, aryl, heteroaryl and/or may contain nitrogen, oxygen, sulfur, halogens and include, for example, lower alkoxy such as methoxy, ethoxy, butoxy, halogen such as chloro or fluoro, nitro, amino, and keto.

The term "taxane" or "taxane core" refers to moieties with a framework of the structure:



The cyclopropane group which can be constituted from R^7 and R^{19} of formula I can alternatively be referred to as "7b,8b-methano" group as in Tetrahedron Letters, Vol 35, No 43, pp 7893-7896 (1994) or as "cyclopropa" group as in U.S. Patent No. 5,254,580 issued October 19, 1993.

The new products that have the general formula I display a significant inhibitory effect with regard to abnormal cell proliferation, and have therapeutic properties that make it possible to treat patients who have pathological conditions associated with an abnormal cell proliferation. The pathological conditions include the abnormal cellular proliferation of malignant or non-malignant cells in various tissues and/or organs, including, non-limitatively, muscle, bone and/or conjunctive tissues; the skin, brain, lungs and sexual organs; the lymphatic and/or renal system; mammary cells and/or blood cells; the liver, digestive system, and pancreas; and the thyroid and/or adrenal glands. These pathological conditions can also include psoriasis; solid tumors; ovarian, breast, brain, prostate, colon, stomach, kidney, and/or testicular cancer, Karposi's sarcoma; cholangiocarcinoma; choriocarcinoma; neuroblastoma; Wilm's tumor, Hodgkin's disease; melanomas; multiple myelomas; chronic lymphocytic leukemias; and acute or chronic granulocytic lymphomas. The novel products in accordance with the invention are particularly useful in the treatment of non-Hodgkin's lymphoma, multiple myeloma, melanoma, and ovarian, urothelial, oesophageal, lung, and breast cancers. The products in accordance with the invention can be utilized to prevent or delay the appearance or reappearance, or to treat these pathological conditions. In addition, the compounds of formula I are useful in treating and/or preventing polycystic kidney diseases (PKD) and rheumatoid arthritis.

The compounds of this invention can be made by techniques from the conventional organic chemistry repertoire. Schemes I - VI, which depict processes that compounds within the scope of formula I can be made, are only shown for the purpose of illustration and are not to be construed as limiting the processes to make the compounds by any other methods.

The preparation of a diol intermediate **4** is shown in Scheme I. The starting material is a taxane analog suitably protected to leave the most reactive hydroxy group at C-7. Compound **1** in Scheme I is protected at the 2' hydroxy group at the sidechain with a triethylsilyl ether. The preparation of intermediates such as **1** are now well known in the art. The synthesis of diol **4** utilizes precursor 6,7-olefin analogs **3** which is also now well known in the art. Compound **3** can be formed directly from intermediate's **1** upon treatment with a reagent such as DAST as described in the U.S. patent 5,380,751. The synthesis of olefin **3** described in Scheme I proceeds through the 7-trifluoromethanesulfonate (triflate) intermediates **2** which are prepared as shown in step A. Elimination of the triflate (step B) provides the desired olefins **3**. The preparation of 7-O triflates and their conversion into cyclopropanes and olefins has been divulged by Johnson, R.A., *et al., Taxol chemistry. 7-O-Triflates as precursors to olefins and cyclopropanes. Tetrahedron Letters,* **1994.** *35*(43): p. 7893-7896 & by the same authors in WO 94/29288.

The olefin **3** is then hydroxylated with Osmium tetroxide (step C) which is used in either stoichiometric quantities or catalytically in the presence of a cooxidant such as N-methyl morpholine-N oxide (NMO). A patent application on such diol intermediates which includes some methods of its preparation has been published: Roth et. al. 6,7 EP 0 600 517 A1 . A protected taxane diol intermediate has also been described in the literature by Liang et. al. *Tetrahedron Letters* **1995,** *36(17)* 2901-2904. and *ibid.* **1995,** *36(43)* 7795-7798. The osmium reagent only reacts from the face of the double bond which is down or alpha as the taxane core is depicted in this document. Thus this reaction provides only one stereoisomer.

The preferred approach to the initial 7-deoxy-substituted taxanes is shown in Scheme II. An advantage of this approach is it avoids the need for a selective protection of the starting 6,7 diol **4**. A new cyclic thiocarbonate **5** is formed (step D)upon reaction with thiocarbonyldiimidazole (or alternatively thiophosgene could be used) under standard conditions of amine base and optional inert solvent. Other standard organic chemistry bases could also be utilized. Reduction of the thiocarbonate **5** (step E) with most preferably, a trialkyl germane such as tri-n-butyl germane provides the C-7 deoxy compound **6** with

little, if any, competitive formation of the C-6 deoxy material. Alternatively, a trialkyl tin hydride could be utilized in place of the germanium reagent. The use of the tin hydride reagent also results in competitive deoxygenation at C-10 which produces mixtures which must be separated. The tin reagent is the method of choice for producing C 7 and 10 deoxy -6-substituted analogs if these are the desired targets. The use of trialkyl germane to suppress an unwanted side reaction is not precedented. This reagent has been studied by physical chemists in other radical reactions. J. W. Wilt et.al. *J. Am. Chem. Soc.* **1988**,*110*, 281-287. The product of step E is a 7-deoxy-6-alpha- hydroxy intermediate **6** which is protected at the sidechain.

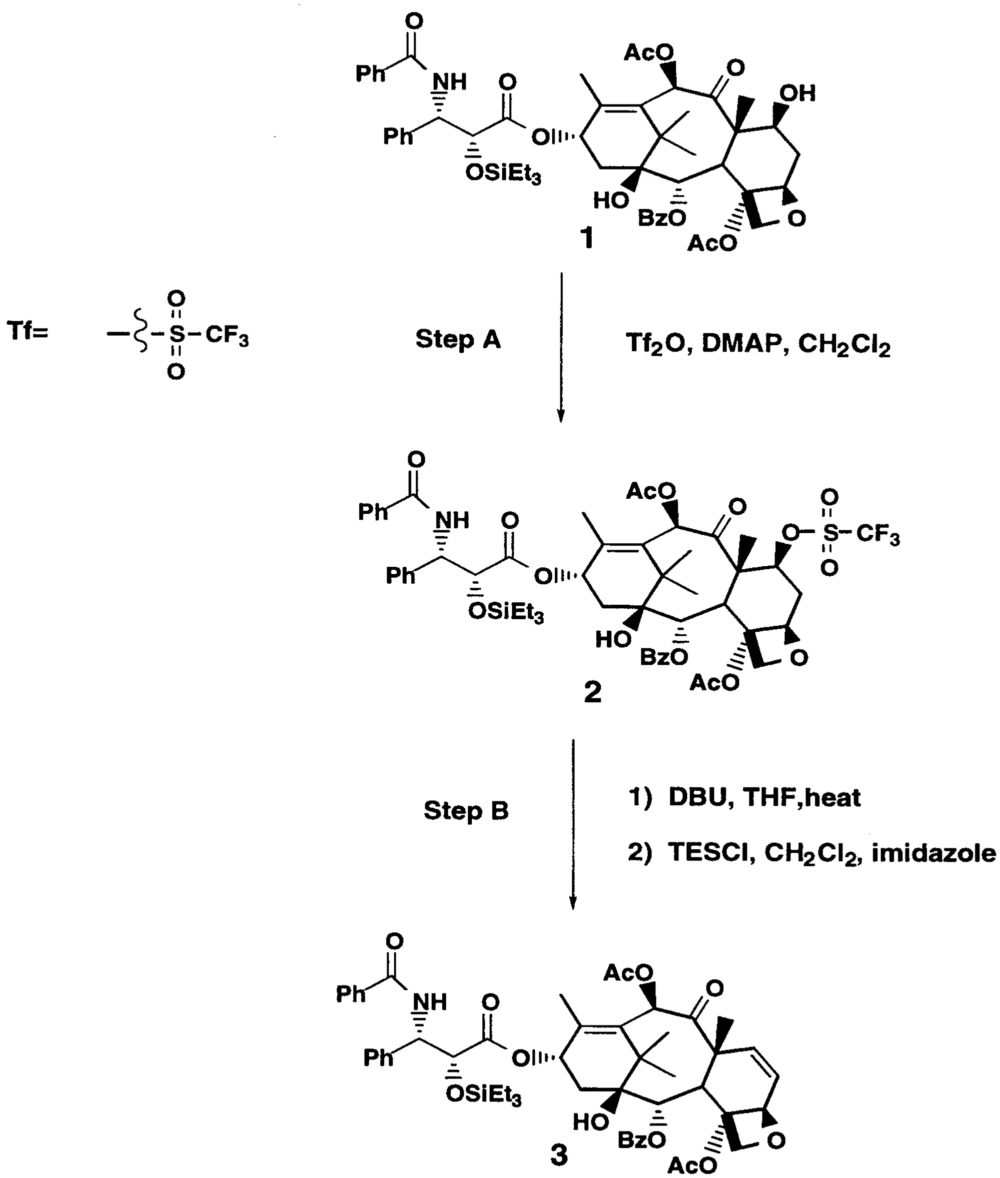
Scheme III illustrates the preparation of the C-6 trifluoromethanesulfonate (triflate or Tf) **7** from the C-6 hydroxy compound **6**. The conversion is carried out as shown in Step f using Triflic anhydride and 4-N,N-Dimethylamino pyridine (DMAP) as a catalyst. Although other amine bases could be utilized, the conditions described in the experimental are preferred. While a number of nonprotic organic solvents can be utilized successfully for this reaction, the preferred solvent is dichloromethane.

Scheme IV, step G illustrates a direct displacement of the trifluromethanesulfonate of Compound **7** to produce the imidazolide Compound **8.** This reaction illustrates the use of heterocyclic compounds which contain an NH group as nucleophiles to displace the triflate grouping. As shown in step H of Scheme IV, the 2' trialkylsilyl protecting group present in Compound **8** can be removed using triethylamine trihydrofluoride in THF to provide **Ia** which is a compound claimed in this invention. These are standard conditions for removing silyl protecting groups from taxanes and other standard conditions could also have been utilized.

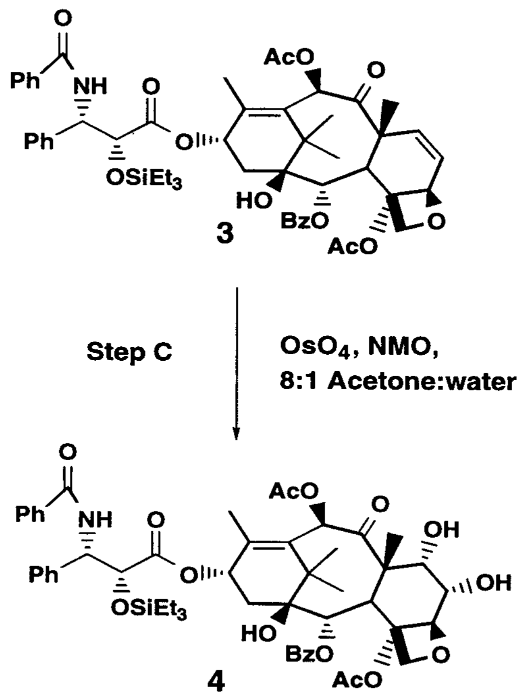
Scheme V, step I illustrates the use of azide ion as a nucleophile to give Compound **9.** In UK patent application GB 2,296,239A 6-azido structures are claimed but in all cases a 7-hydroxyl group is present. In the present invention the C-7 position is deoxygenated which provides a unique activity advantage. The trialkylsilyl group can be removed as in step H above to give Compound **Ib** which is a compound claimed in this

invention. Compound **9** serves as the starting material for the preparation of C-6 derivatives **Ic** an **Id** as illustrated in Scheme VI steps J and K.

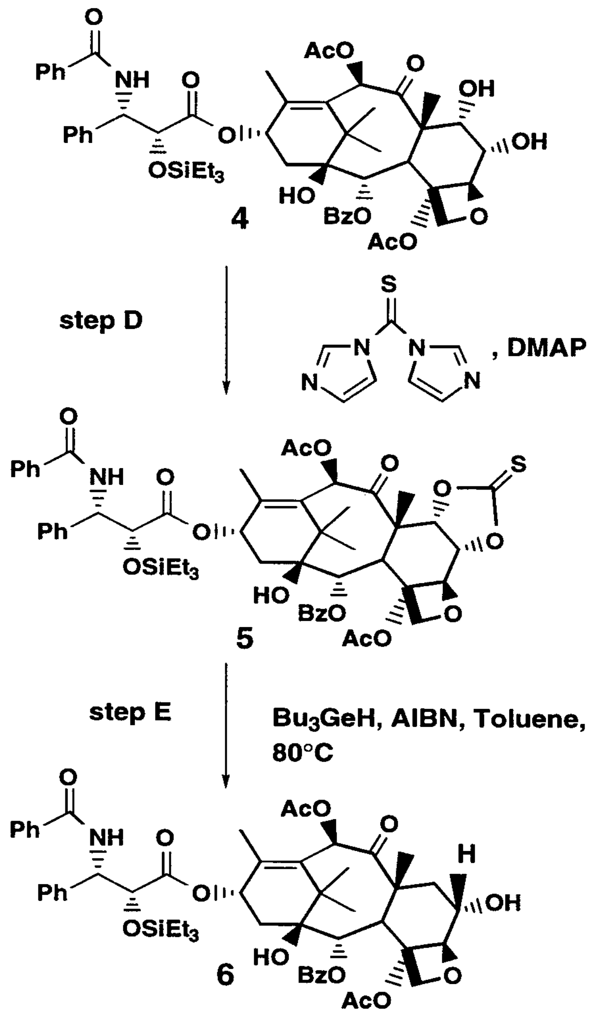
Scheme I


1
Tf=
Step A
Tf$_2$O, DMAP, CH$_2$Cl$_2$
2
Step B
1) DBU, THF,heat
2) TESCl, CH$_2$Cl$_2$, imidazole
3

Scheme I continued



Scheme II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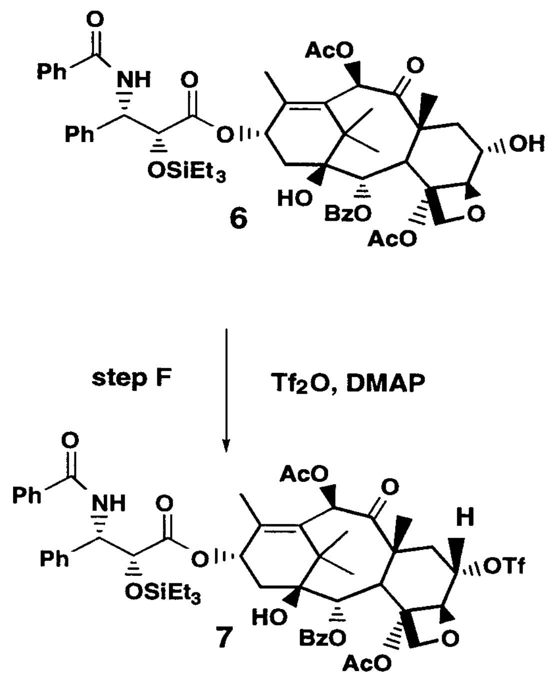
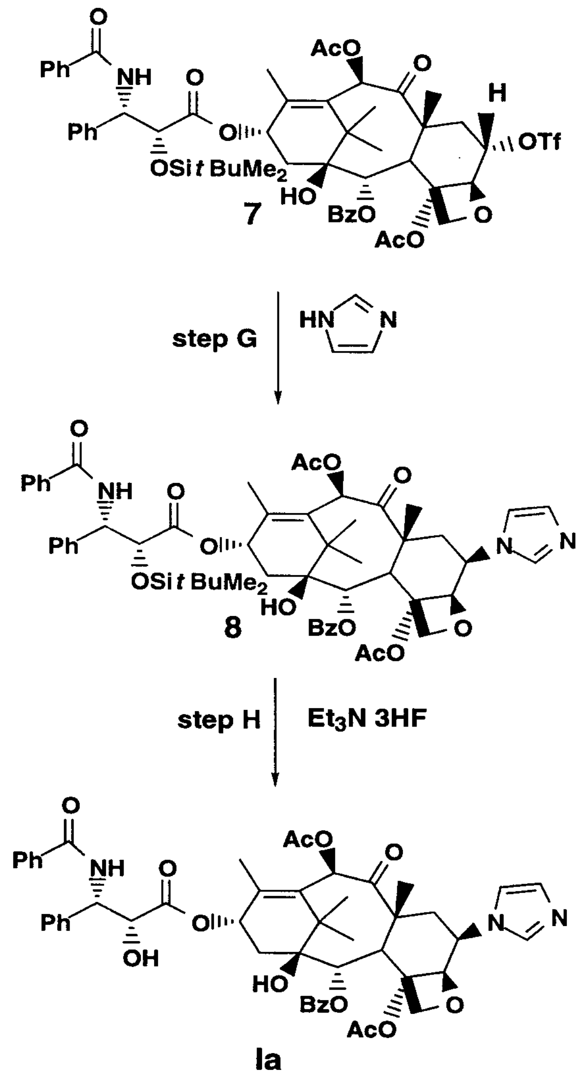
Scheme III



Scheme IV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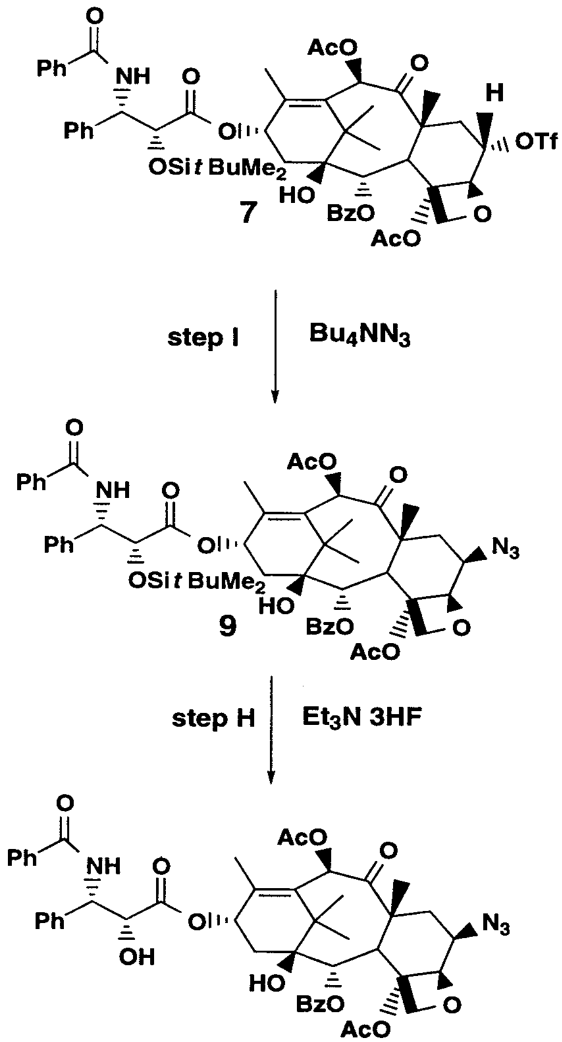
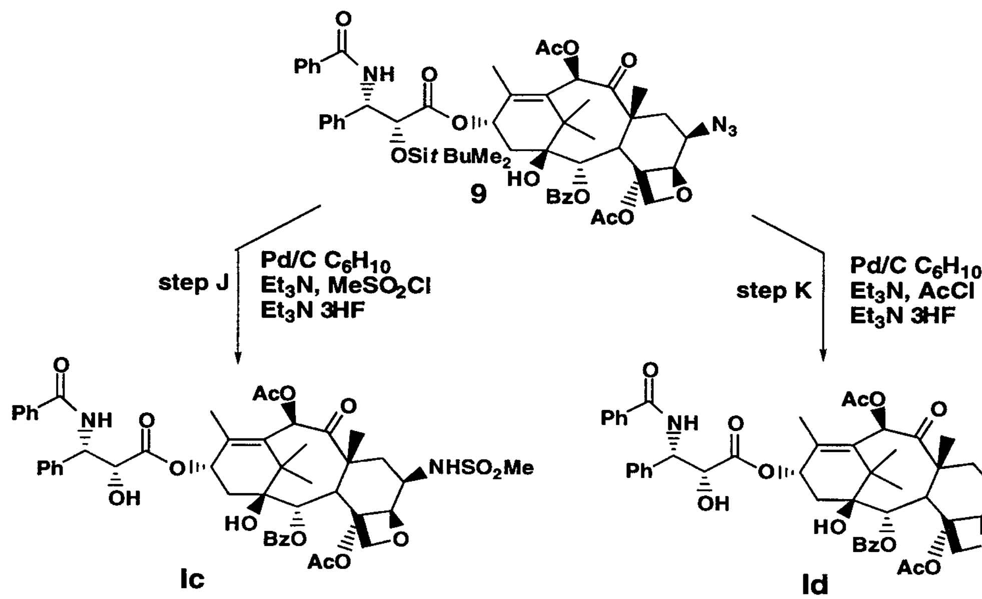
Ia

Scheme V



Ib

Scheme VI



The examples above describe compounds containing a paclitaxel sidechain. It is well known in the art that chemistry that works with a paclitaxel sidechain works with other standard sidechains or on baccatin III analogs which contain a suitably protected C-13 hydroxy group. Examples of suitable C-13 protecting groups include trialkylsilyl, TROC , or phenoxy acetate.

Some of the schemes refer to a hydroxy protecting group, preferably trialkylsilyl group. It is to be understood that hydroxy protecting group may be a carbonate or ester group -C(O)OR^{x} or -C(O)R^{x}. Thus when such a group is employed as a hydroxy protecting group, it may either be removed to generate the free hydroxy protecting group or it may remain as a part of the final product.

By now there are many publications teaching the introduction of a wide variety of groups onto a taxane core. By using these well established methods or obvious variants thereof, the starting taxanes of formula I, or hydroxy protected analogues thereof, can be readily made. For example, for transforming C4-acetoxy into other functional groups see, S. H. Chen et al., *J. Organic Chemistry*, 59, pp 6156-6158 (1994) and PCT application

WO 94/14787 published July 7, 1994; for converting C2-benzoyloxy to other groups see, S.H. Chen et al, *Bioorganic and Medicinal Chemistry Letters*, Vol. 4, No. 3, pp 479-482 (1994); K.C. Nicolaou et al., *J. Am. Chem. Soc.*, 1995, 117, 2409 and European Patent Application 617,034A1 published September 28, 1994; for modifying C10-acetyloxy see, K.V. Rao et al., *J. Med. Chem.*, **38**, pp 3411-3414 (1995), J. Kant et al., *Tetrahedron Letters*, Vol. 35, No. 31, pp 5543-5546 (1994); and U.S. Patent No. 5,294,637 issued March 15, 1994; for making C10 and/or C7 unsubstituted (deoxy) derivatives see, European Patent Application 590,267A2 published April 6, 1994 and PCT application WO 93/06093 published April 1, 1993; for making C-10 epi hydroxy or acyloxy compounds see PCT application WO 96/03394; for making C-10 deoxy-C-10 alkyl analogs see PCT application WO95/33740; for making 7b,8b-methano, 6a,7a-dihydroxy and 6,7-olefinic groups see, R. A. Johnson, *Tetrahedron Letters*, Vol. 35, No 43, pp 7893-7896 (1994), U.S. Patent No. 5,254,580 issued October 19, 1993, and European Patent Application 600,517A1 published June 8, 1994; for making C7/C6 oxirane see, X. Liang and G.I. Kingston, *Tetrahedron Letters*, Vol. 36, No. 17, pp 2901-2904 (1995); for making C7-epi-fluoro see, G. Roth et al, *Tetrahedron Letters*, Vol 36, pp 1609-1612 (1995); for forming C7 esters and carbonates see, U.S. Patent No. 5,272,171 issued December 21, 1993 and S. H. Chen et al., *Tetrahedron*, 49, No. 14, pp 2805-2828 (1993); for 9a- and 9b-hydroxy taxanes see, L. L. Klein, *Tetrahedron Letters*, Vol 34, No 13, pp 2047-2050 (1993), PCT application WO 94/08984 published April 28, 1994, U.S. Patent No. 5,352,806 issued October 4, 1994, PCT application WO 94/20485 published September 15, 1994, and G.I. Georg et. al. . *Tetrahedron Letters*, Vol 36, No 11, pp 1783-1786 (1995).

DESCRIPTION OF SPECIFIC EMBODIMENTS

The specific examples that follow illustrate the syntheses of the compounds of the instant invention, and is not to be construed as limiting the invention in sphere or scope. The method may be adapted to variations in order to produce the compound embraced by this invention but not specifically disclosed. Further, variations of the methods to produce the same compound in somewhat different manner will also be evident to one skilled in the art.

In the following experimental procedures, all temperatures are understood to be in Centigrade (C) when not specified. The nuclear magnetic resonance (NMR) spectral characteristics refer to chemical shifts (d) expressed in parts per million (ppm) versus tetramethylsilane (TMS) as reference standard. The relative area reported for the various shifts in the proton NMR spectral data corresponds to the number of hydrogen atoms of a particular functional type in the molecule. The nature of the shifts as to multiplicity is reported as broad singlet (bs or br s), broad doublet (bd or br d), broad triplet (bt or br t), broad quartet (bq or br q), singlet (s), multiplet (m), doublet (d), quartet (q), triplet (t), doublet of doublet (dd), doublet of triplet (dt), and doublet of quartet (dq). The solvents employed for taking NMR spectra are acetone-d_6 (deuterated acetone). DMSO-d_6 (perdeuterodimethylsulfoxide), D_2O (deuterated water), $CDCl_3$ (deuterochloroform) and other conventional deuterated solvents. The infrared (IR) spectral description include only absorption wave numbers (cm^{-1}) having functional group identification value.

Celite is a registered trademark of the Johns-Manville Products Corporation for diatomaceous earth.

The abbreviations used herein are conventional abbreviations widely employed in the art. Some of which are: DAB (deacetylbaccatin III); MS (mass spectrometry); HRMS (high resolution mass spectrometry); Ac (acetyl); Ph (phenyl); v/v (volume/volume); FAB (fast atom bombardment); NOBA (m-nitrobenzyl alcohol); min (minute(s)); h or hr(s) (hour(s)); DCC (1,3-dicyclohexylcarbodiimide); BOC (t-butoxycarbonyl); CBZ or Cbz (benzyloxycarbonyl); Bn (benzyl); Bz (benzoyl); Troc (2,2,2-trichloroethyloxycarbonyl), DMS (dimethylsilyl), TBAF (tetrabutylammonium fluoride), DMAP (4-dimethylaminopyridine); TES (triethylsilyl); DMSO (dimethylsulfoxide); THF (tetrahydrofuran); HMDS (hexamethyldisilazane); MeOTf (methyltriflate); NMO (morpholine-N-oxide); $(DHQ)_2PHAL$ (hydroquinine 1,4-phthalazinediyl diether). Tf = triflate = trifluoromethanesulfonate; LRMS (low resolution mass spectrometry); ESI (electrospray ionization).

<u>Preparation of Starting Materials (Scheme I)</u>

2'-O-(triethylsilyl)-paclitaxel [1]

Paclitaxel (15g, 17.57 mmol) was dissolved in a solution of 60mL of pyridine and 60mL of dichloromethane and then the mixture was cooled to 0°C. Triethylsilyl chloride (11.8mL, 70.3 mmol) and the reaction was stirred for 90 min at 0°. The reaction was diluted with ethyl acetate, washed successively with water and then brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography over silica gel using 2:1 hexane/ethyl acetate as eluent to provide 17.0g (99%) of the title compound.

2'-O-(t-butyldimethylsilyl)-paclitaxel [1a]

Paclitaxel (146.0 mg, 0.17 mmol) was dissolved in dry N,N-dimethylformamide (1 mL). To this solution imidazole (116.1 mg, 1.7 mmol) and t-butyldimethylsilyl chloride (128.8 mg, 0.85 mmol) were added successively and the mixture was stirred at 60°C for 1 hour. The reaction mixture was then diluted with ethyl acetate (2 mL), followed by water. The aqueous layer was washed with additional ethyl acetate (2 X 2 mL). The combined organic layers were then washed with water and brine, dried over sodium sulfate, and evaporated to give crude product. Purification of the crude product by preparative TLC (silica gel, 7:3 hexane : ethyl acetate) furnished 2'-O-(t-butyldimethylsilyl)-paclitaxel (157 mg, 95% yield).

2'-O-(triethylsilyl)-7b-O-trifluoromethanesulfonylpaclitaxel [2]

The alcohol **1** (17g, 17.5 mmol) and DMAP (8.55g, 70mmol) was dissolved in dichloromethane and then the mixture was cooled to 0°C. Trifluoromethanesulfonic anhydride (3.39mL, 20.1 mmol) was added via syringe and then reaction was allowed to warm to ambient temperature. The reaction was stirred for 2 hours, was diluted with ethyl acetate, washed successively with water and then brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography over silica gel using 2:1 hexane/ethyl acetate as eluent to provide 17.6g (91%) of the title compound.

2'-O-(*t*-Butyldimethylsilyl)-7b-O-trifluoromethanesulfonylpaclitaxel [2a]
2'-O-(*t*-butyldimethylsilyl)paclitaxel **[1a]** (180.0 mg, 0.19 mmol) was dissolved in dry CH_2Cl_2 (2 mL). To this solution 4-dimethylaminopyridine (61.0 mg, 0.5 mmol) and trifluoromethanesulfonyl chloride (50 mL, 0.5 mmol) were added successively at 0°C and the mixture was stirred at room temperature for 1 hour. Then to this solution addtional 4-dimethylamino pyridine (61.0 mg, 0.5 mmol) and trifluoromethanesulfonyl chloride (50 mL, 0.5 mmol) were added successively and the mixture was stirred at room temperature for additional 1.5 hours. The reaction mixture then was diluted with EtOAc (4.0 mL) and the precipitate was filtered off on Celite. The solvent was evaporated, and the residue was purified by preparative TLC (silica gel, 6:4 hexane : EtOAc) to furnish 2'-O-(t-butyldimethylsilyl)-7-O-trifluoromethanesulfonylpaclitaxel (187.0 mg, 92% yield). ^1H NMR ($CDCl_3$, TMS, 400 MHz) d 8.12 (d, 2H), 7.73 (d, 2H), 7.60 (t, 1H), 7.53-7.30 (m, 10H), 7.09 (d, 1H, J = 8.9, H_{NH}), 6.62 (s, 1H, H_{10}), 6.25 (t, 1H, J = 9.2, H_{13}), 5.76 (q, 1H, J = 8.9, 2.6, $H_{3'}$), 5.74 (d, 1H, J = 7.0, H_2), 5.49 (dd, 1H, J = 7.5, 10.1, H_7), 4.94 (d 1H, J = 8.6, H_5), 4.67 (d, 1H, J = 2.0, $H_{2'}$), 4.37 (d, 1H, J = 8.5, H_{20}), 4.22 (d, 1H, J = 8.5, H_{20}), 3.97 (d, 1H, J = 7.0, H_3),2.85 (m,1H, H_6) 2.60 (s, 3H, $-CH_3$), 2.39 (m, 1H, H_{14}), 2.19 (s, 3H, $-CH_3$), 2.18 (m, 2 H, H_6, H_{14}), 2.08 (s, 3H, $-CH_3$), 1.89 (s, 3H, $-CH_3$), 1.22 (s, 3H, $-CH_3$), 1.18 (s, 3H, $-CH_3$), 0.8 (s, 9H), -0.02 (s, 3H), -0.29 (s, 3H). ^{13}C NMR ($CDCL_3$, TMS, 100 MHz) d 200. 97, 171.89, 171.16, 169.34, 167,71, 167.42, 141.75, 138.77, 134.66, 134,45,133.48, 132.46, 130.84, 129.52, 129.47, 129.40, 129.38, 128.65, 127.59, 127.00, 86.39, 83.68, 80.64, 79.25, 76.94, 75.77, 75.74, 74.92, 71.69, 57.97, 56.23, 47.55, 43.75, 36.32, 34.67, 26.76, 26.23, 26.13, 23.47, 22.01, 21.29, 18.75, 14.87, 14.80, 11.538, -4.54, -5.20. LRFABMS *m/z* calcd for $C_{54}H_{65}NO_{16}F_3SiS$ $[MH]^+$ 1100, found 1100.

2'-O-(triethylsilyl)-6,7-dehydropaclitaxel [3]
The triflate **2** (17.6g, 16mmol) was dissolved in 75 mL of dry THF and then 12.18g (80mmol) of DBU was added. The reaction was heated at reflux for 2 hours and then diluted with ethyl acetate. The organic layer was washed five times with water and then brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude product was dissovled in methylene chloride and then 16 mmol of imidazole and 8 mmol of triethylsilyl chloride were added. The reaction was stirred for 1.5h at ambient temperature, diluted with ethyl acetate, washed with two

portions of water, dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude material was purified by flash chromatography over silica gel using 2:1 hexane/ethyl acetate as eluent to provide 15.0g (99%) of the title compound.

2'-O-(t-butyldimethylsilyl)-6,7-dehydropaclitaxel [3a]

To a stirred solution of 2'-(t-butyldimethylsilyl)-7b-trifluoromethanesulfonylpaclitaxel **[2a]**, (202.0 mg, 0.18mmol) in dry dichloromethane (1.0 mL) was added 1,8-diazabicyclo (5,4,0) undec-7-ene (DBU, 300.0 mL, 2.0 mmol). The mixture was kept stirring at 40°C for 4 hours. The reaction mixture then was diluted with ethyl acetate (2.0 ml) and washed with diluted HCl, diluted $NaHCO_3$ solution, water and brine. The aqueous layer was extracted with additional ethyl acetate (2 X 2 mL). The combined organic layers were dried over sodium sulfate and evaporated to give crude product. Purification of the crude product by preparative silica gel TLC (7:3 hexane : ethyl acetate) furnished two compounds: 2'-(t-butyldimethylsilyl)-6,7-dehydropaclitaxel **[3b]** (150.0 mg, 86%) and 6,7-dehydropaclitaxel (21.3 mg, 13.9%). Spectoscopic data for **3b**: ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz) d 8.12 (d, 2H), 7.73 (d, 2H), 7.60 (t, 1H), 7.53-7.30 (m, 5H), 7.07 (d, 1H, *J* = 8.9, H_{NH}), 6.24 (s, 1H, H_{10}), 6.25 (t, 1H, *J* = 9.2, H_{13}), 6.08 (dd,1H, *J* =9.9, 5.6, H_6), 5.87 (d, 1H, *J* = 9.9, H_7), 5.86 (d, 1H, *J* = 6.5, H_2), 5.72 (d, 1H, *J* = 8.6, $H_{3'}$), 5.12 (d 1H, *J* = 5.5, H_5), 4.65 (d, 1H, *J* = 2.0, $H_{2'}$), 4.45 (d, 1H, *J* = 8.1, H_{20}), 4.34 (d, 1H, *J* = 8.1, H_{20}), 4.03 (d, 1H, *J* = 6.5, H_3), 2.58 (s, 3H, $-CH_3$), 2.44 (m, 1H, H_{14}), 2.22 (s, 3H, $-CH_3$), 2.18 (m, 2 H, H_6, H_{14}), 1.88 (s, 3H, $-CH_3$), 1.83 (s, 3H, $-CH_3$), 1.24 (s, 3H, $-CH_3$), 1.14 (s, 3H, $-CH_3$), 0.79 (s, 9H), -0.05 (s, 3H), -0.32 (s, 3H). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) d 205.44, 171.32, 169.56, 169.39, 166.91, 166.87, 141.60, 140.03, 138.27, 134,06,133.67, 133.61, 131.76, 130.19, 129.16, 128.80, 128.73, 128.71, 128.69, 127.92, 126.96, 126.36, 126.126, 81.22, 81.12, 76.31, 75.82, 75.64, 75.12, 71.23, 60.36, 55.65, 55.40, 35.98, 26.29, 25.49 23.14, 22.12, 22.02, 20.744, 20.46, 18.09, 14.62, 14.17, -5.28, -5.89. LRFABMS *m/z* calcd for $C_{53}H_{64}NO_{13}Si$ $[MH]^+$ 950, found 950.

2'-O-(triethylsilyl)-6a-hydroxy-7-*epi*-paclitaxel [4]

The olefin **3** was dissolved in 180mL of acetone and 22.5 mL of water. NMO (4.06g, 34.74 mmol) was added and the reaction was stirred for 12 days. Silica gel was added and the reaction was concentrated in vacuo to provide a near free flowing powder which was placed on top of a flash

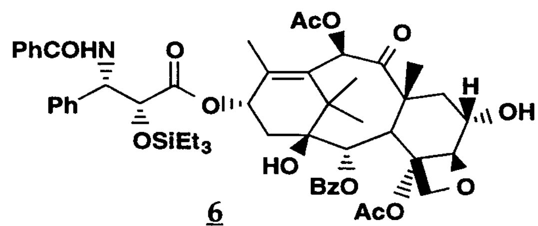
chromatography silica gel column. Elution with 1:1 hexane/ ethyl acetate provided 13.35g (86%) of the desired diol.

2'-O-(t-Butyldimethylsilyl)-6a-hydroxy-7-*epi*-paclitaxel [4a]

To a solution of 2'-O-(*t*-butyldimethylsilyl)-6,7-dehydropaclitaxel [**3a**], (60.0 mg, 0.063 mmol) in THF (500 mL, 10 drops H_2O) were added osmium tetraoxide (2.5 wt. 2.5% solution in 2-methyl-2-propanol, 150 mL, 0.015 mmol) and 4-methyl morpholine-N-oxide (NMO, 50 mg, 0.42 mmol). The mixture was kept stirring at room temperature for 4 hours. Additional osmium tetraoxide solution (150 mL, 0.015 mmol) was then added to the reaction mixture to accelerate the reaction. The reaction mixture was kept stirring at room temperature for additional 5 hours. To the reaction solution was added sodium bisulfite (25 mg) and the mixture was stirred for 10 minutes, then diluted with EtOAc (1 mL), filtered through Celite, and washed with H_2O and brine. The aqueous layer was extracted with additional EtOAc (2 X 2 mL). The combined organic layers were dried over Na_2SO_4 and evaporated. Isolation of the residue on preparative TLC plate (silica gel, 1:1 hexane : EtOAc) furnished starting material (7.2 mg, 12%) and a more polar compound 2'-O-(t-butyldimethylsilyl)-6a-hydroxy-7-*epi*-paclitaxel [**4b**] (48.0 mg, 78% yield). ^1H NMR ($CDCl_3$, TMS, 400 MHz) d 8.15 (d, 2H), 7.70 (d, 2H), 7.64-7.26 (m, 6H), 7.07 (d, 1H, J = 8.8, H_{NH}), 6.83 (s, 1H, H_{10}), 6.29 (t, 1H, J = 8.8, H_{13}), 5.79 (q, 1H, J = 8.8, 2.4, $H_{3'}$), 5.74 (d, 1H, J = 7.6, H_2), 4.71 (d, 1H, J = 12.0, $H_{7\text{-}OH}$), 4.68 (d, 1H, J = 2.0, H_5), 4.66 (bs, 2H, H_{20}), 4.36 (s, 1H, $H_{2'}$), 4.18 (m, 1H, H_6), 3.87 (d, 1H, J = 7.6, H_3), 3.70 (q, 1H, J = 5.2, 12.0, H_7), 2.90 (d, 1H, J = 8.2, $H_{6\text{-}OH}$), 2.62 (s, 3H, $-CH_3$), 2.42-2.10 (m, 2H, H_{14}), 2.18 (s, 3H, $-CH_3$), 1.90 (s, 3H, $-CH_3$), 1.62 (s, 3H, $-CH_3$), 1.18 (s, 3H, $-CH_3$), 1.12 (s, 3H, $-CH_3$), 0.78 (s, 9H), -0.03 (s, 3H), -0.3 (s, 3H). HRFABMS *m/z* calcd for $C_{47}H_{52}NO_{15}$ $[MH]^+$ 870.3337, found 870.3336.

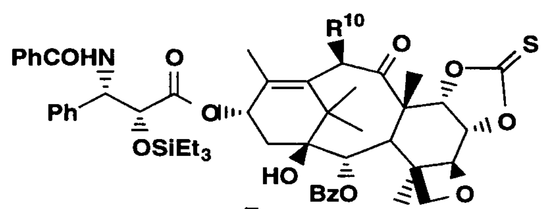
Example 1

Preparation of 2'-O-(triethylsilyl)-7-deoxy-6a-hydroxypaclitaxel [6]-(Scheme II)



6

The diol **4** (1.773g, 1.809 mmol), thiocarbonyldiimidazole(0.996 g, 5.427 mmol), DMAP(0.618 g, 5.065 mmol) were dissolved in 50 mL THF and allowed to stir overnight. The reaction was diluted with EtOAc, washed with $NaHCO_3$, and brine. The solution was dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed over silica gel (1:1 hexane/ethyl acetate) to yield 1.646 g of product **5** (89%).



5

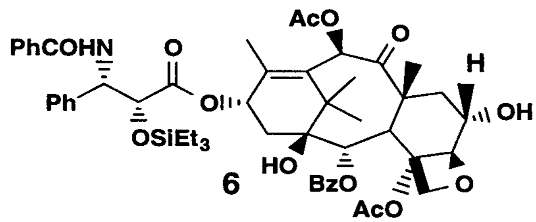
ESILRMS M+NH_4^+calcd. for $C_{54}H_{63}O_{15}N_2S$ Si: 1043. Found: 1043.

Anal. calcd. for $C_{54}H_{63}O_{15}N$ S Si: C, 63.20; H, 6.19; N, 1.36. Found: C, 63.04; H, 6.22; N, 1.33.

IR(KBr) 3438(br.), 2958, 1746, 1717,1282, 1236 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz) d 8.15(d, J= 7.2 Hz, 2H), 7.74(d, J= 7.2 Hz, 2H), 7.63-7.32(m, 11H), 7.12(d, J= 9.0 Hz, 1H), 6.87(s, 1H), 6.25(br. t., 1H), 5.83(d, J= 6.9Hz, 1H), 5.70(d, J= 9.0, 1H), 4.97(d, J= 11.4 Hz, 1H), 4.87(s, 1H), 4.72(m, 2H), 4.39(d, J= 8.1 Hz, 1H), 4.22(d, J= 8.1 Hz, 1H), 4.00(D, J= 6.9 Hz, 1H), 2.57(s, 3H), 2.43-2.35(m, 1H), 2.21(s, 3H), 2.16-2.08(m, 1H), 2.03(m, 4H), 1.87(s, 3H), 1.21(s, 3H), 1.17(s, 3H), 0.79(m, 9H), 0.44(m, 6H).

The thiocarbonate **5** (0.200 g, 0.196 mmol), AIBN(cat.), (aza-isobutyrylnitrile (catalytic)) and Bu_3GeH(0.479 g, 1.96 mmol) were dissolved in 3 mL toluene under Argon. The reaction mixture was frozen, dried *in vacuo*, and thawed three times to remove O_2. The reaction was heated to 85°C for 1 hr.. The reaction mixture was concentrated and chromatographed over silica gel (1.5:1 hexane/ethyl acetate) to yield 0.137 g of product **6** (72%).



6

ESILRMS M+H calcd for $C_{53}H_{65}O_{14}N$ Si: 968. Found: 968.

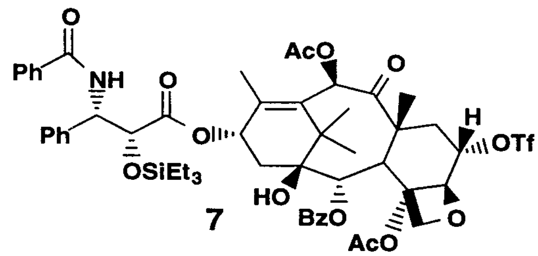
Anal. calcd. for $C_{53}H_{65}O_{14}NSi\text{-}H_2O$: C, 64.55; H, 6.85; H, 1.42. Found: C, 64.49; H, 6.82; N, 1.41.

IR(KBr) 3442(br.), 2956, 1734, 1486, 1372, 1244, 710 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz) d 8.13(d, J= 8.7 Hz, 2H), 7.72(d, J= 8.4 Hz, 2H), 7.62-7.33(m, 11H), 7.10(d, J= 8.7 Hz, 1H), 6.45(s, 1H), 6.24(t, J= 8.7 Hz, 1H), 5.71-5.64(m, 2H), 4.80(s, 1H), 4.66(d, J= 2.1 Hz, 1H), 4.31(d, J= 8.4 Hz, 1H), 4.18-4.14(m, 2H), 3.78(d, J= 7.5 Hz, 1H), 2.54(s, 3H), 2.48-2.39(m, 1H), 2.20(s, 3H), 2.17-2.08(m, 1H), 2.02(d, J= 9.0 Hz, 2H), 1.90(s,4H), 1.77(s,1H), 1.71(s, 3H), 1.19(s, 3H), 1.10(s, 3H), 0.79(m, 9H), 0.41(m,6H).

Example 2

Preparation of 2'-O-(triethylsilyl)-7-deoxy-6α-triflouromethanesulphonyloxypaclitaxel [7]-(Scheme IV)



The alcohol **6** (0.950 g, 0.98 mmol) and DMAP (0.479 g, 3.92 mmol) were dissolved in 10 mL of dichloromethane and cooled to 0°C under nitrogen. Triflic anhydride (198 μL, 1.18 mmol) was added via syringe, and the reaction was allowed to stir at 0°C for 10 min. The crude reaction mixture was placed directly onto a vacuum funnel containing a 1.5 inch plug of silica gel wet with hexanes, and eluted with (3:1 hexanes / ethyl acetate) to provide the triflate **7** (0.842 g 78%) as a white powder.

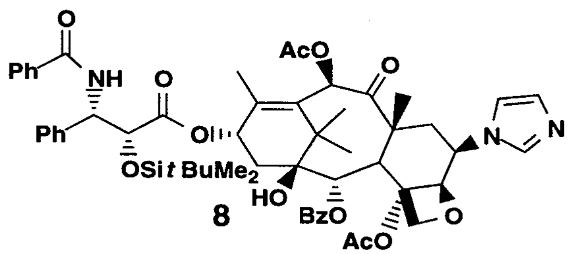
ESIMS *m/z* 1099 (M-H)

IR (KBr) 3442, 2957, 1748, 1735, 1725, 1245, 1225, 1143 cm^{-1}

^{1}H NMR ($CDCl_3$ 300 MHz) δ: 8.13 (d, J=7.2 Hz, 2H), 7.72 (d, J=7.2 Hz, 2H), 7.50-7.25 (m, 11H), 7.10 (d, J = 9.1Hz, 1H), 6.41 (s, 1H), 6.25 (t, J = 8.6Hz, 1H), 5.73 (d, J = 9.0Hz, 1H), 5.64 (d, J = 7.5Hz, 1H), 5.22 (dd, J = 11.7, 7.5Hz, 1H), 4.98 (s, 1H), 4.68 (d, J = 2.0Hz, 1H), 4.33 (d, J = 8.5Hz, 1H), 4.26 (d, J = 8.6Hz, 1H), 3.89 (d, J = 7.4Hz, 1H), 2.58 (s, 3H, 2.50-2.40 (m, 2H), 2.21 (s, 3H), 2.19-2.04 (m, 2H), 1.92 (s, 3H), 1.71 (s, 3H), 1.21 (s, 3H), 1.10 (s, 3H), 0.78 (m, 9H), 0.43 (m, 6H)

Example 3

Preparation of 2'-O-(*t*-Butyldimethylsilyl)-7-deoxy-6β-imidazoylpaclitaxel [8]-(Scheme IV)



8

To a solution of the 6α-triflate **7** (604 mg, 0.549 mmol) in 20 mL of toluene was added imidazole (374 mg, 5,49 mmol) and the solution heated at 110°C for 90 minutes. The solution was cooled and diluted with ethyl acetate and washed with water and brine and dried over $MgSO_4$. The solution was concentrated and the residue chromatographed over silica gel using hexane/ ethyl acetate (1:1) to give 467 mg of imidazolide **8** (83%).

ESIMS *m/z* 1018 (M+H)

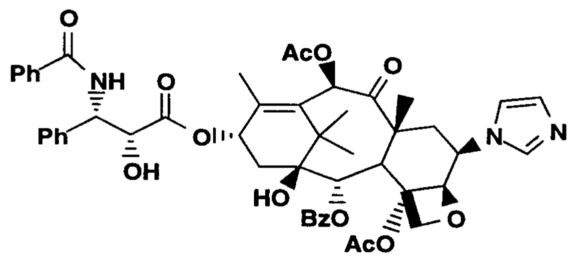
IR (KBr) 1744, 1731, 1723, 1270, 1240, 1108 cm^{-1}

^1H NMR ($CDCl_3$ 300 MHz) δ: 8.13 (d, J=7.2 Hz, 2H), 7.74 (d, J=7.2 Hz, 2H), 7.61-7.25 (m, 12H), 7.06 (d, J = 9Hz, 1H), 7.01 (s, 1H), 6.96 (s, 1H), 6.47 (s, 1H), 6.28 (t, J = 9Hz, 1H), 5.84 (d, J=6.3Hz, 1H), 5.76 (dd, J=9, 1.8 Hz, 1H), 4.98 (m, 2H), 4.69 (d, J=1.8 Hz, 1H), 4.42 (d, J=8.4 Hz, 1H), 4.29 (d, J=8.4 Hz, 1H), 3.97 (d, J=6 Hz, 1H), 2.58 (s, 3H), 2.42-2.39 (m, 2H), 2.38 (s, 3H), 2.36-2.29 (m, 2H), 2.24 (s, 3H), 1.95 (s, 3H), 1.68 (s, 1H), 1.24 (s, 3H), 1.13 (s, 3H), 0.79 (s, 9H), -0.21 (s, 3H), -0.29 (s, 3H).

Anal. Calcd for $C_{56}H_{67}N_3O_{13}Si$: C, 66.06; H, 6.63; N, 4.13. Found: C, 65.95; H, 6.69; N, 4.05.

Example 4

Preparation of 7-deoxy-6β-imidazoylpaclitaxel [Ia]-(Scheme IV)



Ia

To a solution of the imidazolide **8** (396 mg, 0.389 mmol) in 50 mL of THF was added Et_3N 3HF (0.127 mL, 0.779 mmol) and the solution stirred for 24 hours. The solution was diluted with ethyl acetate and washed with water, brine, and dried over $MgSO_4$. The solution was concentrated and the residue crystalized from ethanol/hexane to give 263 mg of **Ia** (75%).

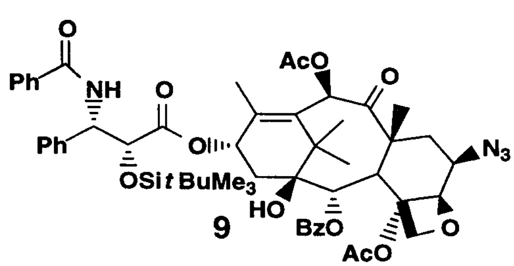
ESIMS *m/z* 904 (M+H)

IR (KBr) 3417, 1729, 1718, 1272, 1237, 1107, 1093, 1074 cm^{-1}

^1H NMR (d_6 acetone, 300 MHz) δ: 9.13 (s, 1H), 8.13 (d, J=7.2 Hz, 2H), 7.98 (d, J=7.2 Hz, 2H), 7.70-7.21 (m, 14H), 6.50 (s, 1H), 6.16 (t, J=9Hz, 1H), 5.83 (d, J=6.3 Hz, 1H), 5.75 (d, J=5.1 Hz, 1H), 5.56 (m, 1H), 5.39 (d, J=3.6 Hz, 1H), 4.86 (d, J=5.1 Hz, 1H), 4.45 (d, J=7.8 Hz, 1H), 4.31 (d, J-7.8 Hz, 1H), 3.98 (d, J=6.3 Hz, 1H), 3.35 (d, 1H), 2.62 (dd, J=15.3, 5.7Hz, 1H), 2.47 (s, 3H), 2.41-2.12 (m, 4H), 2.21 (s, 3H), 2.05 (s, 3H), 1.91 (s, 3H), 1.21 (s, 3H), 1.13 (s, 3H).

Example 5

Preparation of 2'-O-(*t*-Butyldimethylsilyl)-7-deoxy-6β-azidopaclitaxel [9]-(Scheme V)



9

To a solution of the 6α-triflate **7** (268 mg, 0.243mmol) in 5 mL of THF was added Bu_4NN_3 (68 mg, 0.299 mmol) and stirred for 24 hours. The solution was concentrated and the residue chromatographed over silica gel using hexane/ diethyl ether (1:1) to give 226 mg of azide (94%).

ESIMS *m/z* 993 (M+H)

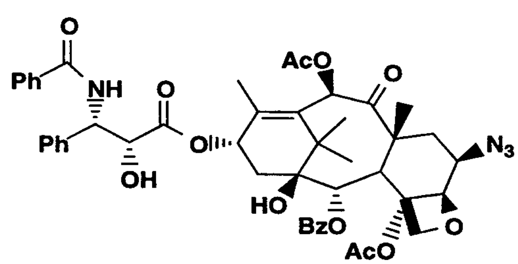
IR (KBr) 3441, 2108, 1750, 1731, 1721, 1242 cm^{-1}

^1H NMR ($CDCl_3$ 300 MHz) δ: 8.20 (d, J=7.2 Hz, 2H), 7.77 (d, J=7.2 Hz, 2H), 7.68-7.36 (m, 11H), 7.11 (d, J = 9 Hz, 1H), 6.50 (s, 1H), 6.30 (t, J = 9Hz, 1H), 5.79 (m, 2H), 5.08 (d, J=7.2 Hz, 1H), 4.70 (d, J=1.8Hz, 1H), 4.46 (d, J=8.4 Hz, 1H), 4.24 (d, J=8.4 Hz, 1H), 4.22 (m, 1H), 3.73 (d, J=6.9 Hz, 1H), 2.63 (s, 3H), 2.47-2.34 (m,2H), 2.26 (s, 3H), 2.16 (dd, J=15.3, 8.7 Hz, 1H), 1.93 (s, 3H), 1.86 (m, 1H), 1.64 (s, 4H), 1.26 (s, 3H), 1.17 (s, 3H), 0.84 (s, 9H), 0.00 (s, 3H), -0.25 (s, 3H).

Anal. Calcd for $C_{53}H_{64}N_4O_{13}Si$: C, 64.09; H, 6.49; N, 5.64. Found: C, 64.23; H, 6.43; N, 5.40.

Example 6

Preparation of 7-deoxy-6β-azidopaclitaxel [Ib]-(Scheme V)



Ib

To a solution of the 2'-TBS ether **9** (445 mg, 0.45 mmol) in 10 mL of THF was added Et_3N 3HF (0.124 mL, 0.765 mmol) and the solution stirred for 24 hours. The solution was diluted with ethyl acetate and washed with water, brine, and dried over $MgSO_4$. The solution was concentrated and the residue crystallized from ethanol/hexane to give 394 mg of **Ib** (quant).

ESIMS *m/z* 877 (M-H)

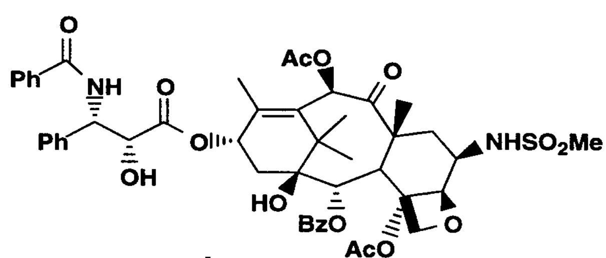
IR (KBr) 3432, 2108, 1731, 1718, 1240 cm^{-1}

^{1}H NMR ($CDCl_3$ 300 MHz) δ: 8.13 (d, J=7.2 Hz, 2H), 7.71 (d, J=7.2 Hz, 2H), 7.64-7.25 (m, 11H), 7.00 (d, J = 9 Hz, 1H), 6.41 (s, 1H), 6.19 (t, J = 9Hz, 1H), 5.77 (dd, J=9, 2.4 Hz, 1H), 5.71 (d, J=6.9 Hz, 1H), 4.99 (d, J=6.9 Hz, 1H), 4.76 (m, 1H), 4.38 (d, J=8.4 Hz, 1H), 4.17 (d, J=8.4 Hz, 1H), 4.14 (m, 1H), 3.67 (d, J=6.6 Hz, 1H), 3.58 (d, J=4.8Hz, 1H), 2.39 (s, 3H), 2.31 (m, 3H), 2.21 (s, 3H), 1.86 (s, 3H), 1.82 (m, 1H), 1.75 (s, 4H), 1.20 (s, 3H), 1.12 (s, 3H).

Anal. Calcd for $C_{47}H_{50}N_4O_{13}$: C, 64.23; H, 5.75; N, 6.37. Found: C, 64.10; H, 5.70; N, 6.11.

Example 7

Preparation of 7-deoxy-6β-methanesulfonamidopaclitaxel [Ic]-(Scheme VI)



Ic

To a solution of the silyl protected azide **9** (290 mg, 0.305 mmol) in 3 mL of ethanol and 3 mL of cyclohexene was added Pearlman's catalyst (48 mg) and the solution heated to reflux for 2 hours. The catalyst was removed by filtration and the filtrate concentrated and dissolved in 5 mL of THF. To the filtrate in THF was added triethylamine (65μL, 0.469 mmol) and methanesulfonyl chloride (28μL, 0.363 mmol) and the solution stirred at 0 °C for 30 minutes and then at ambient temperature for 2 hours. The solution was diluted with ethyl acetate and washed with saturated bicarbonate solution and brine, and dried over $MgSO_4$. The solution was concentrated and the residue chromatographed over silica gel using hexane/ ethyl acetate (1.5:1) to give 134 mg of product (42%).

The residue in 5 mL of THF was stirred for 24 hours with Et_3N 3HF (35µL) diluted with ethyl acetate and washed with water and brine. The solution was dried over $MgSO_4$, concentrated and the residue chromatographed over silica gel using ethyl acetate/ hexane (2:1) to give 99 mg of product (83%) which was crystalized from ethyl acetate/ hexane to give 105 mg of a white amorphous solid.

ESIMS *m/z* 929 (M-H)

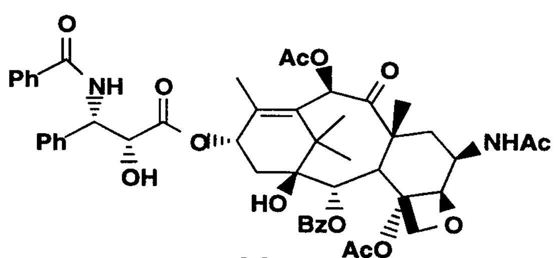
IR (KBr) 3434, 1733, 1720, 1240 cm^{-1}

^1H NMR ($CDCl_3$ 300 MHz) δ: 8.14 (d, J=7.2 Hz, 2H), 7.71 (d, J=7.2 Hz, 2H), 7.64-7.24 (m, 11H), 6.95 (d, J = 9 Hz, 1H), 6.41 (s, 1H), 6.19 (t, J = 9Hz, 1H), 5.77 (dd, J=9, 2.5 Hz, 1H), 5.66 (d, J=6.9 Hz, 1H), 5.05 (d, J=9 Hz, 1H), 4.93 (d, J=8.4 Hz, 1H), 4.78 (m, 1H), 4.13 (m, 2H), 3.61 (d, J=7.2 Hz, 1H), 3.53 (d, J=5.1 Hz, 1H), 2.88 (s, 3H), 2.44-2.39 (m, 3H), 2.39 (s, 3H), 2.19 (s, 3H), 1.86 (s, 1H), 1.79 (s, 3H), 1.74 (s, 3H), 1:19 (s, 3H), 1.11 (s, 3H).

Anal. Calcd for $C_{48}H_{54}N_2O_{15}S$: C, 61.92; H, 5.85; N, 3.01. Found: C, 62.13; H, 5.81; N, 2.75.

Example 8

Preparation of 7-deoxy-6β-acetimidopaclitaxel [Id]-(Scheme VI)



Id

To a solution of the silyl protected azide **9** (280 mg, 0.294 mmol) in 3 mL of ethanol and 3 mL of cyclohexene was added Pearlman's catalyst (48 mg) and the solution heated to reflux for 1 hour. The catalyst was removed by filtration and the filtrate concentrated and dissolved in 5 mL of THF. To the filtrate in THF was added triethylamine (61µL, 0.44 mmol) and acetyl chloride (20µL, 0.35 mmol) and the solution stirred at 0 °C for 30

minutes and then at ambient temperature for 2 hours. The solution was diluted with ethyl acetate and washed with saturated bicarbonate solution and brine, and dried over $MgSO_4$. The solution was concentrated and the residue chromatographed over silica gel using hexane/ ethyl acetate (1:1) to give 165 mg of product (58%).

The residue in 5 mL of THF was stirred for 24 hours with Et_3N 3HF (48μL) diluted with ethyl acetate and washed with water and brine. The solution was dried over $MgSO_4$, concentrated and the residue crystalized from ethyl acetate/ hexane to give 125 mg of a white amorphous solid (82%).

ESIMS *m/z* 912 ($M+NH_4$)

IR (KBr) 3422, 1734, 1718, 1239 cm^{-1}

^1H NMR ($CDCl_3$ 300 MHz) δ: 8.14 (d, J=7.2 Hz, 2H), 7.72 (d, J=7.2 Hz, 2H), 7.64-7.31(m, 11H), 6.98 (d, J = 9 Hz, 1H), 6.43 (s, 1H), 6.19 (t, J = 9Hz, 1H), 6.04 (d, J=8.1 Hz, 1H), 5.78 (dd, J=9, 2.4 Hz, 1H), 5.67 (d, J=7.2 Hz, 1H), 4.92 (d, J=8.4 Hz, 1H), 4.78 (s, 1H), 4.63 (dd, J=15.9, 8.1 Hz, 1H), 4.40 (d, J=8.4 Hz, 1H), 4.14 (d, J=8.4 Hz, 1H), 3.65 (d, J=6.9 Hz, 1H), 3.53 (br s, 1H), 2.38 (s, 3H), 2.36-2.20 (m, 3H), 2.18 (s, 3H), 1.92 (s, 3H), 1.79 (s, 3H), 1.76 (s, 3H), 1.69 (d, J=15 Hz, 1H), 1.19 (s, 3H), 1.12 (s, 3H).

Anal. Calcd for $C_{49}H_{54}N_2O_{14}$: C, 65.76; H, 6.08; N, 3.13. Found: C, 65.48; H, 6.07; N, 2.94.

The compounds of this invention exhibit antitumor activities in in vivo and/or in vitro models. For example, the following test describes the in vitro test used to evaluate some representative compounds of this invention.

Cytoxicity

The epoxide taxane derivatives possessed cytoxicity *in vitro* against human colon carcinoma cells HCT-116. Cytoxicity was assessed in HCT-116 human colon carcinoma cells by MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulphenyl)-2H-tetrazolium, inner salt) assay as reported in T.L. Riss, et. al., "Comparison of MTT, XTT, and a

novel tetrazolium compound MTS for in vitro proliferation and chemosensitivity assays.," *Mol. Biol. Cell* 3 (Suppl.):184a, 1992. Cells were plated at 4,000 cell/well in 96 well microtiter plates and 24 hours later drugs were added and serial diluted. The cells were incubated at 37° form 72 hours at which time the tetrazolium dye, MTS at 333 μg/ml (final concentration), in combination with the electron coupling agent phenazine methosulfate at 25 μM (final concentration) was added. A dehydrogenase enzyme in live cells reduces the MTS to a form that absorbs light at 492nM which can be quantitated spectrophotometrically. The greater the absorbance the greater the number of live cells. The results are expressed as an IC_{50}, which is the drug concentration required to inhibit cell proliferation (i.e. absorbance at 450nM) to 50% of that of untreated control cells. The IC_{50} values for compounds evaluated in this assay are evaluated in Table I.

Table I.

Compound	Cytotoxicity Assay IC_{50} (nM) against HCT 116 Human colon tumor cell line[1]
Ia example 4	2.45
Ib example 6	0.63
Ic example 7	>107
Id example 8	25.9
paclitaxel	1.53-2.73

[1]Cytoxicity was determined after a 72 h exposure by MTS assay.

Thus, another aspect of the instant invention concerns a method for inhibiting human and/or other mammalian tumors which comprises administering to a tumor bearing host an antitumor effective amount of a compound of formula I.

For treating a variety of tumors, the compound of formula I of the present invention may be used in a manner similar to that of paclitaxel, e.g. see Physician's Desk Reference, 49th Edition, Medical Economics, p 682, 1995. The dosage, mode and schedule of administration for the compound of this invention are not particularly restricted; an oncologist skilled in the art of cancer treatment will be able to ascertain, without undue experimentation, an appropriate treatment protocol for

administering the compound of the present invention. Thus the compound of formula I may be administered via any suitable route of administration, parenterally or orally. Parenteral administration includes intravenous, intraperitoneal, intramuscular, and subcutaneous administration.

The doses utilized to implement the methods in accordance with the invention are the ones that make it possible to administer prophylactic treatment or to evoke a maximal therapeutic response. The doses vary, depending on the type of administration, the particular product selected, and the personal characteristics of the subject to be treated. In general, the doses are the ones that are therapeutically effective for the treatment of disorders caused by abnormal cell proliferation. The products in accordance with the invention can be administered as often as necessary in order to obtain the desired therapeutic effect. Some patients may respond rapidly to relatively high or low doses, and then require mild maintenance or no maintenance dose at all. Via the iv route, the dosage may be, for example, in the range of about 20 to about 500 mg/m^2 over 1 to 100 hours. Via the oral route, the dosage may be in the range of 5-1000mg/kg/day of body weight. The actual dose used will vary according to the particular composition formulated, the route of administration, and the particular site, host and type of tumor being treated. Many factors that modify the action of the drug will be taken into account in determining the dosage including age, weight, sex, diet and the physical condition of the patient.

The present invention also provides pharmaceutical formulations (compositions) containing an antitumor effective amount of compound of formula I in combination with one or more pharmaceutically acceptable carriers, excipients, diluents or adjuvants. The compositions can be prepared in accordance with conventional methods. Examples of formulating paclitaxel or derivatives thereof may be found in, for example, United States Patents Nos. 4,960,790 and 4,814,470, and such examples may be followed to formulate the compound of this invention. For example, compound of formula I may be formulated in the form of tablets, pills, powder mixtures, capsules, injectables, solutions, suppositories, emulsions, dispersions, food premix, and in other suitable forms. It may also be manufactured in the form of sterile solid

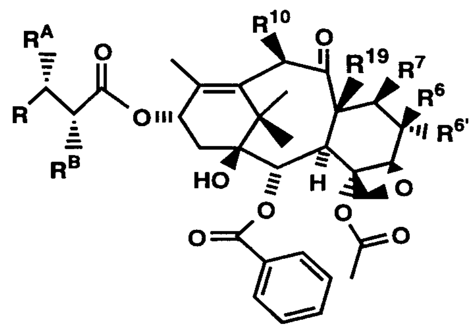
compositions, for example, freeze dried and, if desired, combined with other pharmaceutically acceptable excipients. Such solid compositions can be reconstituted with sterile water, physiological saline, or a mixture of water and an organic solvent, such as propylene glycol, ethanol, and the like, or some other sterile injectable medium immediately before use for parenteral administration.

Typical of pharmaceutically acceptable carriers are, for example, manitol, urea, dextrans, lactose, potato and maize starches, magnesium stearate, talc, vegetable oils, polyalkylene glycols, ethyl cellulose, poly(vinylpyrrolidone), calcium carbonate, ethyl oleate, isopropyl myristate, benzyl benzoate, sodium carbonate, gelatin, potassium carbonate, silicic acid. The pharmaceutical preparation may also contain nontoxic auxiliary substances such as emulsifying, preserving, wetting agents, and the like as for example, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene monostearate, glyceryl tripalmitate, dioctyl sodium sulfosuccinate, and the like.

CLAIMS

What is claimed is:

1. A compound of formula I, or a pharmaceutically acceptable salt thereof



I

wherein R is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, cyclic 3-7 membered ring containing either one or two heteroatoms, heteroaryl or $-Z^1-R^3$;

Z^1 is a direct bond, C_{1-6} alkyl, or $-O-C_{1-6}$ alkyl;

R^3 is aryl, substituted aryl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, cyclic 3-7 membered ring containing either one or two heteroatoms, or heteroaryl;

R^A is -NHC(O)R, -NHC(O)OR, -NHC(O)NHR, $-NHC(O)N(R)_2$, $-NHS(O)_mR$, $-NHP(=O)(OR)_2$, $-NHP=S(OR)_2$, where m is 1 or 2;

R^B is hydroxy, fluoro, $-OC(O)R^x$, $-OC(O)OR^x$, $OP(O)(OH)_2$, $OCH_2OP(O)(OH)_2$, $-OCH_2OCH_2OP(=O)(OH)_2$, $OP(O)(OH)_2$ base, $OCH_2OP(O)(OH)_2$ base, $-OCH_2OCH_2OP(= O)(OH)_2$ base, $-(OCH_2)_mOC=OCH_2NHR^x$, $-(OCH_2)_mOC(=O)CH(R'')NR'_6R'_7$ where m is 0-3, $-OCOCH_2CH_2NH_3^+$ $HCOO^-$, $-OCOCH_2CH_2COOH$, $-OCO(CH_2)_3COOH$, $-OC(O)(CH_2)_nNR^FR^G$, where n is 0-3, $-OC(O)CH_2CH_2C(O)OCH_2CH_2OH$ or -OC(O)-Z-C(O)-R';

Z is ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$), $-CH{=}CH-$, 1,2-cyclohexane or 1,2-phenylene;

R′ is -OH, -OH base, $-NR'_2R'_3$, $-OR'_3$, $-SR'_3$ or $-OCH_2C(O)NR'_4R'_5$;

R'_2 is -H or $-CH_3$;

R'_3 is $-(CH_2)_nNR'_6R'_7$ or $(CH_2)_nN^+R'_6R'_7R'_8X^-$, where n is 1-3;

R'_4 is -H or $-C_1$-C_4 alkyl;

R'_5 is -H, $-C_1$-C_4 alkyl, benzyl, hydroxyethyl, $-CH_2CO_2H$ or dimethylaminoethyl;

R'_6 and R'_7 are independently -H, $-CH_3$, $-CH_2CH_3$, benzyl or R'_6 and R'_7 together with the nitrogen of $NR'_6R'_7$ form a pyrrolidino, piperidino, morpholino, or N-methylpiperizino group;

R'_8 is $-CH_3$, $-CH_2CH_3$ or benzyl;

X^- is halide;

base is NH_3, $(HOC_2H_4)_3N$, $N(CH_3)_3$, $CH_3N(C_2H_4)_2NH$, $NH_2(CH_2)_6NH_2$, N-methylglucamine, NaOH or KOH;

R^F and R^G are independently -H or $-C_1$-C_3 alkyl, or R^F and R^G taken together with the nitrogen of NR^FR^G form a pyrrolidino, piperidino, morpholino or N-methylpiperizino groups;

R″ is -H, $-CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2$phenyl, $-(CH_2)_3NH_2$, $-(CH_2)_4NH_2$, $-CH_2CH_2COOH$, $-(CH_2)_3NHC(=NH)NH_2$, the residue of the amino acid proline, $-OC(O)CH{=}CH_2$, $-C(O)CH_2CH_2C(O)NHCH_2CH_2SO_3$-Y+ or $-OC(O)CH_2CH_2C(O)NHCH_2CH_2CH_2SO_3$-Y+;

Y+ is Na+ or $N+(Bu)_4$;

R^6 and $R^{6'}$ are independently hydrogen, N_3, NH_2, NHR, $N(R)_2$, NHC(O)R, NHC(O)OR, NHC(O)NHR, $NHC(O)N(R)_2$, $NHSO_2R$, NHS(O)R, $NHPO_2OR$, $NHPO_2NHR$ or NR_aR_b where R_a and R_b together with the nitrogen atom form a heteroaryl ring or a heterocyclic ring;

R^7 is hydrogen;

R^{19} is methyl;

R^{10} is hydrogen, hydroxy, $-OC(O)R^x$, $-OC(O)OR^x$, $-O-C_{1-6}$ alkyl, $-OCH_2OCH_3$, $-OCH_2OCH_2OCH_3$, $-OCH_2OCH_2OCH_2CH_3$, $-OCH_2OCH_2CH_2OCH_3$, $-OCH_2OCH_2CH_2OH$, $-OCH_2SR$, $-OCH_2OCH_2SCH_3$, $-OC(O)NR'_6R'_7$, C_{1-6} alkyl, $-(CH_2)_3C(O)R^x$, $-(CH_2)_3C(O)OR^x$, $-(CH_2)_3CN$,$-OP(O)(OH)_2$, $-OCH_2OP(O)(OH)_2$, $-OCH_2OCH_2OP(O)(OH)_2$, $-(OCH_2)_nOC{=}OCH_2NHR^x$, $-(OCH_2)_nOC(=O)CH(R'')NR'_6R'_7$, where n is 0-3, $-OCOCH_2CH_2NH_3^+$ $HCOO^-$, $-OCOCH_2CH_2COOH$, $-OCO(CH_2)_3COOH$, -OC(O)-Z-C(O)-R', $-OC(O)(CH_2)_nNR^FR^G$ where n is 0-3, or $-OC(O)CH_2CH_2C(O)OCH_2CH_2OH$; and

R^X is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cyclo alkyl, any of which groups can be optionally substituted with one to six of the same or different halogen atoms or with one or more hydroxy groups.

2. A compound of claim 1 wherein:

R is phenyl, p-fluorophenyl, p-chlorophenyl, p-Tolyl, isopropyl, isopropenyl, isobutenyl, isobutyl, cyclopropyl, furyl, or thienyl;

R^A is -NHC(O)Ph, or $-NHC(O)O-(C_{1-6}$ alkyl);

R^B is hydroxy;

R^2 is phenyl;

R^4 is methyl;

R^9 and $R^{9'}$ together form an oxo (keto) group;

R^{10} is hydroxy or $-OC(O)CH_3$; and

R^{19} is methyl.

3. A compound of claim 2 wherein:

R is phenyl or p-fluorophenyl;

R^A is -NHC(O)Ph, NHC(O)O-*t*- butyl or -NHC(O)O-isopropyl;

$R^{6'}$ is hydrogen; and

R^{10} is $-OC(O)CH_3$.

4. A compound of claim 3 wherein:

R^6 is N_3, $NHC(O)CH_3$, $NHS(O)_2CH_3$ or imidazole.

5. A compound of claim 4, wherein:

R^A is -NHC(O)Ph; and

R^6 is imidazole.

6. A compound of claim 4, wherein:

R^A is -NHC(O)Ph; and

R^6 is azide.

7. A compound of claim 4, wherein:

R^A is -NHC(O)Ph; and

R^6 is $NHS(O)_2CH_3$.

8. A compound of claim 4, wherein:

R^A is -NHC(O)Ph; and

R^6 is $NHC(O)CH_3$.

9. A pharmaceutical formulation which comprises an antitumor effective amount of a compound of formula I as claimed in any one of claims 1-8.

10. A method for inhibiting tumor growth in a mammalian host which comprises administering to said mammal a tumor-growth inhibiting amount of a compound of formula I as claimed in any one of claims 1-8.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/25872

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/415, 51/04; C07D 233/02, 233/54, 305/00, 413/00
US CL :548/311.4, 110; 514/397, 449; 549/510, 473

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/311.4, 110; 549/510, 473; 514/397, 449

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Please See Extra Sheet.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,206,221 A (MILLER ET AL.) 03 June 1980, see entire document.	1-10
X	US 4,876,399 A (HOLTON ET AL.) 24 October 1989, see entire document.	1-10
X	US 5,380,751 A (CHEN ET AL.) 10 January 1995, see entire document.	1-10
A	US 5,677,462 A (MAS ET AL.) 14 October 1997, see entire document.	1-10
X, P	US 5,710,287 A (HOLTON ET AL.) 20 January 1998, see entire document.	1-10
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[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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Date of the actual completion of the international search

02 FEBRUARY 1999

Date of mailing of the international search report

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	US 5,840,929 A (CHEN) 24 November 1998, see entire document.	1-10

INTERNATIONAL SEARCH REPORT

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B. FIELDS SEARCHED
Documentation other than minimum documentation that are included in the fields searched:

Chemical Abstract
Index Chemicus
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